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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,223	01/24/2001	Raoul E. Benveniste	015280196310	2782

20350 7590 10/06/2004

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,223	BENVENISTE ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,32,33 and 40-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 32, 33, and 40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 09 April, 2004, has been entered.

Status of the Claims

Claims 17, 32, 33, and 40-46 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

Claims 17, 32, 33, and 40-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain the phrase "sufficient to induce a cell mediated response against said human immunodeficiency virus but below the amount necessary to induce an offsetting humoral response" in reference to the nature of the immune response induced by the inactivated/attenuated HIV immunogen which is vague and indefinite. The precise nature of the immune response generated is not readily manifest to the skilled artisan. Cell-mediated immune responses involve antigen presenting cells (i.e., macrophages) and various T-lymphocyte populations (i.e., $CD4^+$, $CD8^+$). What type of cell-mediated immune response is the immunogen supposed to stimulate? Is it supposed to generate an

antigen-specific CTL response? The claims need to clearly set forth the nature of the cell-mediated immune response, the target cell population(s), the antigen of interest (if appropriate), and preferably the titer. Moreover, the reference to an offsetting humoral response is ambiguous. An attenuated HIV immunogen would be expected to induce both an Ab-based and CTL-based immune response. It has been well-documented that patients infected with HIV generate both types of responses. Accordingly, what is the precise immune response that is encompassed by this phrase? What is the specificity and nature of the response? Are the claims directed toward an env-specific Ab response of a certain titer? Applicants need to clearly and unambiguously set forth the salient characteristics of the immune response.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 32, 33, and 40-46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods of vaccinating humans against HIV infection by administering an immunogen comprising an attenuated form or inactivated form of HIV that induces a protective or therapeutic immune response. Specifically, the immunogen must induce a cell-mediated immune response without inducing an "offsetting" humoral

response. Additional limitations stipulate that the immunogen must comprise an inactivated HIV carrying a NC deletion. The terms vaccine, vaccinate, and vaccinating all have an art-recognized definition and refer to an immunogenic preparation capable of inducing a protective or therapeutic immune response (see Dorland's Illustrated Medical Dictionary, 1988, and Stedman's Medical Dictionary, 1982). Thus, the claimed immunogenic composition used to vaccinate said human must provide some sort of protective or therapeutic immune response that prevents HIV infection or ameliorates the clinical sequelae associated with HIV infection.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the correlates of human protection. To date, the correlates of protective immunity remain to be elucidated. It is not known if neutralizing-antibody, CTL responses, or both humoral and cell-mediated immune responses are required for protection. The specificity and titer of the immune response required for protection has yet to be identified. Accordingly, the skilled

artisan cannot reasonably predict if any putative vaccine composition will be protective in vivo. Although, numerous neutralizing-antibody and CTL epitopes have been identified, however, it is not known which components of the immune response are necessary and sufficient for protection from natural infection. Nothing in the specification addresses this critical issue.

2) The disclosure fails to provide any guidance pertaining to the quasispecies nature of HIV infection. The human immunodeficiency viruses exist as a genotypically/phenotypically complex group of viruses within the same host. It has been estimated that between 10^5 and 10^6 variants are present in any given individual. Viral variants are present in different tissue types, as well as, different locations within the same tissue type. Each variant possesses its own pathogenic properties. This vast genetic variation leads to immune escape and evasion. Any vaccine strategy must take the extraordinary sequence variability and mutation rate of HIV into consideration. However, the specification is silent concerning this caveat.

3) The disclosure fails to provide any guidance pertaining to the factors governing the pathogenesis of HIV-induced disease. The immunopathogenesis of HIV infection is exceedingly complex. Several mechanisms have been proposed to explain disease progression including direct pathogenic effects of the virus, HIV-induced autoimmune responses, and HIV-induced T-cell apoptosis. Non-neutralizing antibodies have been shown to enhance HIV infection. The molecular mimicry of host proteins appears to play a role. Viral peptides have are also capable of suppressing immune cell function. Thus, the choice of immunogen needs to be carefully considered before any putative vaccine is tested. Once again, the disclosure fails to provide any direction concerning these issues.

4) The disclosure fails to provide sufficient guidance from an art-recognized animal model of HIV vaccine development. One of the

major obstacles confronting HIV vaccine development is the lack of a suitable animal model that accurately predicts human vaccine efficacy. While different macaque models are useful for studying immune responses, nevertheless, the numerous structural differences between HIV and SIV preclude the direct translation of macaque vaccine studies to humans. Moreover, the skilled artisan must carefully evaluate any given animal model vaccine study to ensure that suitable challenge viruses are employed. Finally, most animal models fail to test the same vaccine construct or immunogen that will be employed in human studies. Thus, these models are of limited utility. As Feinberg and Moore (2002) conclude, "Animal models cannot determine whether a vaccine will be effective against HIV-1 infection in humans; only Phase III trials in humans can do so."

5) The disclosure fails to provide adequate guidance pertaining to the ability of any given immunogen to induce a cell-mediated immune response without generating a noticeable humoral response. The claimed invention appears to require the induction of a viral-specific CTL response without generating an appreciable antibody response. The claims require an attenuated or inactivated HIV immunogen. It has been well-documented that HIV contains both humoral and CTL epitopes. Moreover, during the course of natural infection, both neutralizing antibody and CTL responses are observed. Thus, it is not readily manifest how applicants intend to induce a CTL response by administering an attenuated or inactivated virus without inducing an antibody response. The disclosure fails to provide any evidence or publications that address this concern. As previously noted, a recent publication (Shearer and Clerici, 1997) clearly noted that "the conditions under which some of these parameters result in a preferential response of one type or the other have not yet been determined." There are several factors governing the immune response to any

given immunogen (i.e., immunogen dose, adjuvant selection, route of immunization, structure of immunogen, type of antigen presenting cells, costimulatory signals, vaccinee genetic background, cytokine environment, vaccinee immunologic status) thereby making the immunization process an empirical one at best. Since all of these factors can influence the immune response, the skilled artisan cannot readily predict how any given putative vaccine will influence the immune response. Extensive testing will be required to ascertain which of the aforementioned parameters are most important. Unfortunately, the disclosure fails to address this point as it applies to humans and putative HIV vaccines.

6) The disclosure fails to provide adequate guidance pertaining to the nature of the immunogen. It has been well-documented in the field that one of the primary problems with HIV vaccine development is that investigators do not know which immunogens, adjuvants, and immunization regimens will produce a protective or therapeutic immune response. The disclosure clearly fails to address any of these issues. This is not surprising considering that the correlates of protective immunity pertaining to HIV-1 infection have not been determined.

7) The state-of-the-art vis-à-vis HIV vaccine development has encountered many difficulties and failures (Hoth *et al.*, 1994; Stott and Almond, 1995; Graham and Wright, 1995; Haynes *et al.*, 1996; Haynes, 1996; Kent *et al.*, 1997; Lee, 1997; Letvin, 1998; Burton and Moore, 1998; Moore and Burton, 1999; Nathanson and Mathieson, 2000; Johnston, 2000; Bende and Johnston, 2000; Feinberg and Moore, 2002). To date, there is no effective vaccine for the prevention or treatment of HIV-1 or -2 infection. Various vaccines that displayed promising results in macaque models have undergone preliminary clinical trials. None of these vaccines have proved efficacious. This is due to a number of factors including the *quasispecies* nature of HIV infection which leads to rapid immune

escape, a lack of understanding of the correlates of protective immunity thereby precluding the identification of suitable viral immunogens, delivery vehicles, and immunization regimens, the lack of suitable animal models in which to assess vaccine efficacy, the ability of the virus to reside in quiescent T-lymphocytes thereby persisting indefinitely, and a lack of understanding of mucosal immune responses. The disclosure fails to provide any illumination on any of these topics.

8) The claims are of considerable breadth and encompass any given immunogen without providing sufficient structural and functional guidance. The generic claims simply require an inactivated or attenuated HIV. The HIV genome is approximately 9.5 kb in length and encodes various structural and regulatory genes. Since the precise immunogen and form that are required to produce a therapeutic or protective immune response remain to be elucidated, the skilled artisan has been asked to guess as to which regions of the genome should be modified to produce a suitably attenuated virus. Moreover, problems with attenuated vaccines include reversion to a more virulent form, even with multiple gene deletions. Considering the unpredictability of the state-of-the-art vis-à-vis HIV vaccine development the skilled artisan would reasonably conclude that the disclosure fails to support the breadth of the claimed invention.

9) The disclosure fails to provide any working embodiments. As noted supra, there are several complications associated with HIV vaccine development. Accordingly, the skilled artisan would reasonably require a working example before practicing the claimed invention. The disclosure is merely prophetic and fails to provide any actual working embodiments.

Thus, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

37 C.F.R. § 1.132

Applicants provided a declaration by Dr. Benveniste under 37 C.F.R. § 1.132 that argues that the macaque model is predictive of human vaccine efficacy. Five references were cited that argue that this is a useful animal model. None of these references demonstrate that data obtained from the SIV model has directly led to the development of an efficacious human vaccine. This model is useful as a preliminary step in vaccine development to study immune response. However, as previously set forth, data obtained from this system cannot be directly extrapolated to humans. Three additional references from the macaque model were cited wherein it was presumably demonstrated that low-dose immunization regimens led to protective CTL responses in macaques. Once again, these publications suffer from the same limitations previously discussed pertaining to the utilization of data obtained from the macaque model. Finally, three additional references are cited to support the contention that HIV-specific CTL responses may be responsible for the lack of disease progression in certain patient populations. While these studies are promising, nevertheless, they fail to provide any significant guidance pertaining to the identification of suitable HIV immunogens. Which immunogens, adjuvants, and immunization regimens can reasonably be expected to provide protection or a therapeutic immune response? What is the specificity and titer any given CTL response that is required for protection? None of these publications reasonably address these critical issues.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be

reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

30 September, 2004